

Medicine Anticounterfeiting Based on an Edible Matrix Code

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A smartphone-readable, edible matrix code composed of fluorescent silk proteins enables patients to verify their own medicines.

With the rapid growth of online pharmacies, the emerging counterfeit medicines industry poses a huge threat to both the global economy and public health. So far, various anticounterfeiting methods have been used to ensure the safety of pharmaceutical products; however, none of these methods enable the patients to verify the authenticity of medicines on their own. In this issue of *ACS Central Science*, Kim and co-workers designed an edible matrix code based on silk fibroin which was genetically hybridized with diverse fluorescent proteins (Figure 1a).¹ In addition, the authors demonstrated the edibility of the matrix code and its capacity for anticounterfeiting at the dose level (Figure 1b).

In their work, the authors confirmed three vital characteristics of the proposed matrix code: first, the code consisted of proteins with edible properties; second, the code was imperceptible and multidimensional, capable of being edited by introducing various fluorescence emission colors; last, patients were able to conveniently verify the authenticity of medicines by scanning the code on their phone.

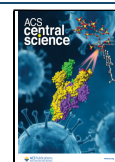
Numerous anticounterfeiting methods for medicines have been developed, such as supply chain management, product packaging, and chemical analysis.^{2,3} However, these methods are usually sophisticated and costly. Most importantly, patients cannot tell if drugs are authentic or fake by themselves using these methods. Advanced anticounterfeit technologies tend to focus on medicines at the dosage level, which means that a security measure is integrated directly into the product itself so that each product can be independently verified and traced.^{4,5} Interestingly, multiple fluorescent color materials have received increasing attention due to their ability to read stored information under external stimuli.^{6–8} To this

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end, the authors chose edible and digestible silk protein as the coding material, which could be recombined with fluorescent proteins (eCFP, eGFP, and mKate2) by the piggyBac transposase method. Therein, the above-mentioned transgenic fluorescent silk fibroin solutions and films exhibited distinct fluorescence emission colors such as cyanic green and red, and each one was available for a unique series of photonic excitation and emission bands. In addition, the recombined fluorescent silk fibroin films showed good photostability under white light illumination that was 10-fold higher than office light.

An anticounterfeiting code is generally concealed to make it invisible to the naked eye.⁹ To fabricate tamper-resistant, relatively transparent anticounterfeiting code, the authors utilized transgenic silk fibroin solutions of three fluorescence emission colors to produce matrix codes on the substrate of white silk fibroin and used a matrix mask with predetermined square openings as a mold to hold the different fluorescent silk protein solutions to form a multidimensional code. The multidimensionality of the three fluorescence colors makes

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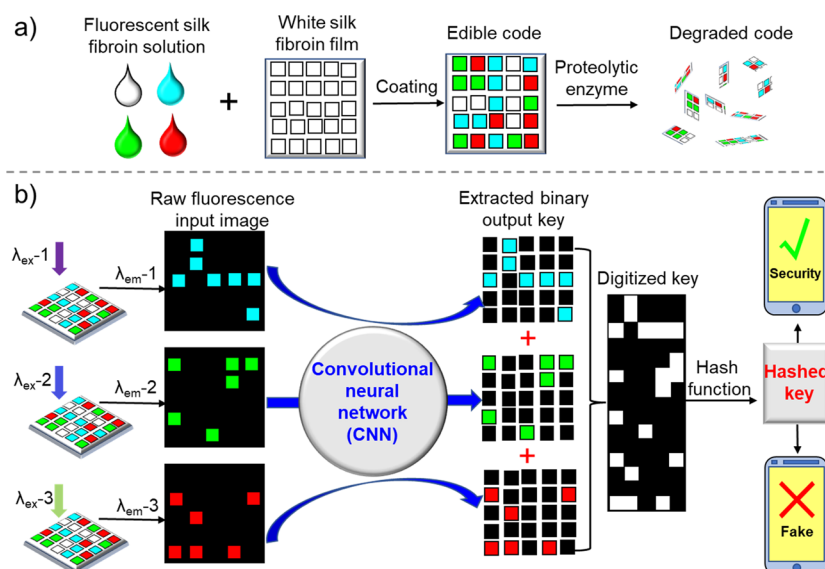


Figure 1. (a) Schematic illustration of the manufacturing process of edible codes combining three different fluorescence emission colors of transgenic silk fibroin solutions and nonfluorescence emission regenerated silk fibroin and their degradation. (b) Schematic illustration of the authenticity verification process of the hash function generated after extracting the digitized code from the fluorescent image of the edible matrix code.

it difficult to tamper with the matrix code. On the other hand, different numbers of matrix arrays could be introduced into the substrate to make the coding capacity variable. What's more, the fluorescent codes were visible only under the optical filter. Also, the invisibility of the code had already been enhanced via patterning with micrografting arrays by means of soft imprint lithography.

Anticounterfeiting technologies are currently restricted to liquid medicines. Therefore, experiments were conducted to test the possibility of using edible codes with medicines in liquid dosage form. Silk fibroin is often treated with alcohol to improve its optical properties,¹⁰ and alcohol is a common ingredient in liquid medicines. Thus, the authors investigated the stability of fluorescent silk fibroin films in liquid alcohol. They found that the fluorescence emission ability of eGFP films was almost unaffected over 6 months of exposure in 0–99% ethanol solutions. Accordingly, the fluorescence silk films did not deform significantly during this period when the concentration of ethanol exceeded 20%. Consequently, the authors speculated that the result was caused by the conversion of random coils into β -sheets, thereby increasing the crystallinity.

Furthermore, in order to ensure that the information stored in the edible code could be accurately extracted, as shown in Figure 1b, the authors designed a 2D convolutional neural network (CCN), which could convert the raw fluorescent input images into a binary bitmap. Then, the input binary bitmap (digitized key) could be transformed into a unique digital signature (hashed key) by a hash function. Importantly, this CCN technology overcame defects in patterns

and shapes that occurred during the fabrication process, significantly enhancing the accuracy of the information extracted.

As a simulation, an edible code was attached to oral dosage tablets, proving the effectiveness of on-dose authentication through a smartphone-based application (app). First, the authors opened a custom-built app with a unique set of filters on their phone, and then they scanned the code, generating a fluorescent matrix pattern. The app automatically identified the pattern of the code, extracting it as a digital key. Finally, the app converted the digital key into the hash key and showed the corresponding hyperlinked webpage to validate the drug. In a similar way, the authors tested an edible code embedded in a high-value wine. The results showed that the authenticity of the wine could be verified without opening it.

In addition to having great anticounterfeiting ability, another key feature of edible codes is that they are degradable

In addition to having great anticounterfeiting ability, another key feature of edible codes is that they are degradable. To evaluate the digestibility of edible codes, the authors investigated the enzymatic degradation rates of fluorescent silk fibroin in 0.1% pepsin and 0.25% trypsin solutions simulating the gastrointestinal environment. eGFP, whose fluorescence is sensitive to denaturation, was used as a simulation to quantify the denaturation and degradation of the protein. After immersing eGFP films in the solutions, the silk fibroin films were seriously damaged by gastric enzymes and the

fluorescence intensity of eGFP in pepsin and trypsin also decreased dramatically after 60 min. These results indicate that protein-based edible codes can be easily digested after oral intake.

On the whole, this successful preparation of an edible, on-dose anticounterfeiting code provides fresh thinking on the topic of drug anticounterfeiting, allowing patients themselves to participate in the process of combating illegal drugs. This will greatly reduce the use of counterfeit drugs for treatment, which are often ineffective and may even cause secondary harm to patients' health, improving the credibility of medicines and public health overall. In addition, the information extraction method of the CCN greatly improved the accuracy of drug authentication and was unaffected by errors caused during the manufacturing process. These advances will have great significance for the commercialization of anticounterfeiting codes. The fibroin codes were demonstrated to be stable in ethanol solution; however, whether they will work with other kinds of liquid medicines remains unknown. We sincerely expect that edible materials for other kinds of liquid medicines and anti-counterfeiting codes will be developed in the foreseeable future. Furthermore, methods to overcome the difficulties of embedding edible codes on solid powdered medicines for on-dose anticounterfeiting are required.

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